In Vivo and *in Vitro* Exposure to PCB 153 Reduces Long-Term Potentiation

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We examined the effects of gestational and lactational exposure to polychlorinated biphenyl (PCB) 153 (2,4,5,2´,4´,5´-hexaCB) on the magnitude of long-term potentiation (LTP) observed in the CA1 region of hippocampal brain slices prepared from rats at 30 days of age. We compared these actions to those observed when PCB 153 is dissolved in normal Krebs-Ringer solution and perfused on slices from control rats of the same age. *In vivo* exposure was at three dose levels (1.25, 5, and 20 mg/kg/day) from gestational day 3 through weaning at postnatal day 21. Although responses to low-frequency stimulation of the Schaffer collateral pathway in exposed animals were not different from controls, significantly reduced LTP was induced after tetanic stimulation, even at the lowest dose studied. We observed a comparable depression of LTP when control slices were perfused with Krebs-Ringer that had been equilibrated with PCB 153 in a generator column. Neither *in vivo* nor *in vitro* exposure significantly altered the input–output curves obtained before tetanic stimulation, but both suppressed the increase in response observed in controls after tetanic stimulation. Because LTP is thought to be correlated with learning ability, these observations may provide at least a partial mechanism to explain the reduction of intelligence quotient observed in humans exposed to PCBs early in development. *Key words*: CA1, generator column, gestational/lactational exposure, hippocampus, *in vitro* exposure, learning. *Environ Health Perspect* 108:827–831 (2000). [Online 27 July 2000]
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Polychlorinated biphenyl (PCB) exposure is correlated with a reduction in intelligence quotient (IQ) in children exposed through gestation and/or lactation in at least two populations. Chen et al. (*1*) studied children in Taiwan exposed in the Yu-Cheng incident (where PCB-contaminated rice oil was used for cooking for a period of time). Children born to exposed mothers, even if born years after the maternal exposure, showed a variety of effects including a downward shift in average IQ of approximately 5 IQ points. This effect appeared not to reverse with the age of the child, suggesting that the effect might be permanent. Because the PCBs were heated during cooking there was some formation of dibenzofurans and thus some uncertainty as to whether observed effects were due to the PCBs, the furans, or both.

The other study with the most convincing demonstration of IQ deficits after PCB exposure is that of Jacobson and Jacobson (*2*). They followed children born to mothers who consumed contaminated fish from Lake Michigan, and reported a 6.2-point IQ deficit in the highest exposure category when the children were studied at 11 years of age. In this study the deficit appeared to be related to prenatal, not postnatal, exposure. Although the fish were also contaminated with other potentially neurotoxic substances, especially methylmercury, the authors suggested that the effect on IQ is secondary to exposure to PCBs. Decrements in neurobehavioral function have also been reported in other exposed human populations (*3,4*) and in exposed monkeys (*5*) and rodents (*6,7*).

Long-term potentiation (LTP) is a prolonged increase in synaptic responses that can be induced in certain neural pathways by a brief tetanic stimulation (*8*). LTP is believed to be at least a component of learning and memory (*9*). LTP is reduced in aged animals (*10*) and is reduced or absent in various mutants that show reduced learning capacity (*11,12*). When LTP in animals is saturated, further learning is impaired (*13*). LTP is blocked by lead (*14,15*), an environmental contaminant that also causes a reduction in IQ. We previously showed (*16*) that acute exposure of hippocampal brain slices of normal rats to PCB mixtures results in a reduction of LTP with exposures that did not significantly alter other aspects of synaptic transmission.

PCB 153 (2,4,5,2´,4´,5´-hexaCB) is a di-*ortho*, nondioxin-like congener that is persistent in both the environment and in the human body. PCB 153 is present in almost every person in significant amounts because of its resistance to degradation. It is one of the three dominant PCB congeners in human adipose tissue (*17*) and is the congener with the highest concentration in breast milk (*18*). Because it is a poor activator of the aryl hydrocarbon (Ah) receptor (*19*) it has generally not been considered particularly hazardous.

We determined the effects of gestational and lactational exposure to PCB 153 at three concentrations and compared those to effects of acute exposure of control rat hippocampal area CA1 slices.

Methods

Timed-pregnant Sprague-Dawley rats (Taconic Farms, Inc., Germantown, NY) were exposed by ingestion to PCB 153 mixed in corn oil and applied daily on a sweet wafer. The rats were dosed from gestational day 7 through postnatal day 21, when the pups were weaned. We synthesized the PCB 153 in our laboratories, and purity was > 99% with no other congeners detected. The possible presence of contaminating furans was tested in the laboratory of Patrick O'Keefe (Wadsworth Laboratories, Albany, NY), and total tetra-, penta-, and hexachlorodibenzofurans (sum of 2,3,7,8- and non-2,3,7,8-substituted congeners) were present at 418, 177, and 15 ppb, respectively. 2,3,7,8-Tetra and 1,2,3,4,7,8-hexachlorodibenzofuran were present at 1.49 and 0.37 ppb, respectively. Chlorinated dibenzodioxins were not present above detection limits of 0.3–1.3 ppb. We exposed dams at four dose levels (0, 1.25, 5.0, and 20.0 mg/kg/day). At birth, litters were culled to eight pups (five males and three females). There were no significant dose-related effects on fertility, birth number, and postnatal growth at these doses. Body weights of PCB-exposed dams were not different from controls. We ran the experiment over a period of 5 weeks in blocks of four dams: one control and one at each exposure level. One male pup (30 ± 3 days of age) from each litter was used in these experiments, and the investigator was blinded to exposure category until the end of the full experimental period. On average we studied three slices of hippocampus per animal. Results were averaged and reported on the basis of per-litter exposure. Thus five animals were used for recording LTP at each dose level in these studies.

We determined LTP in the CA1 region of hippocampal brain slices as previously described (*15,16*). In brief, animals were

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euthanized by cervical dislocation, the brain quickly removed into ice-cold Krebs-Ringer solution [normally containing (in mM) NaCl, 125; KCl, 3.5; KH_2PO_4, 1.2; $MgCl_2$, 1.3; $CaCl_2$, 2.4, $NaHCO_3$, 26; and glucose, 10, pH 7.3] in which all NaCl was replaced with isosmotic sucrose, blocked, and mounted on a vibratome with tissue-binding glue (Konishi, Osaka, Japan). Slices (450-µm thick) were cut and incubated in normal Krebs-Ringer solution for at least 1 hr before being mounted in the recording chamber, submerged, and constantly perfused with Krebs-Ringer. We stimulated the Schaffer collateral pathway at a frequency of 0.033 Hz at a stimulation intensity < 10 V, which gave a response that was approximately 50% maximal and had an amplitude of between 0.7 and 1 mV. After stability of the recording had been obtained [recording for at least 30 min after mounting and a population field excitatory postsynaptic potential (fEPSP) of constant amplitude], we recorded control responses and applied tetanic stimuli consisting of two separate 1-sec stimulations, each at the test intensity at 100 Hz with the two stimulations separated by 5 sec. Input–output curves were obtained before and after tetanic stimulation in slices from animals after *in vivo* exposure by monitoring the amplitude of the fEPSP, reflecting the monosynaptic response generated in many different neurons recorded from the apical dendritic layer as a function of stimulation intensity. We prepared five to six slices per animal, of which it was usually possible to record from three. The LTP amplitude was measured as the percent increase in amplitude at 60 min compared to control and the post-LTP input–output relations were also determined 60 min or more after tetanus.

In animals with *in vivo* exposure the exposure code was broken only after all experiments were completed. For *in vitro* exposure to PCB 153, we prepared a generator column by depositing 200 mg PCB 153 in 50 mL hexane onto glass beads and evaporating it to dryness (*20*). Distilled water was slowly circulated over the beads for a period of not less than 4 days; the beads were then used to make a Krebs-Ringer solution that contained PCB 153 at the limit of its aqueous solubility (reported as 0.91 ppb) (*21*), which is approximately 3 nM. We prepared slices from unexposed male rat pups at 30 days of age as described above and perfused the slices with normal Krebs-Ringer solution. After recording stability was achieved the perfusing solution was changed to the Krebs-Ringer containing PCB 153. This solution was perfused for 15 min before tetanic stimulation to determine effects on baseline synaptic responses, then tetanic stimulation was applied and the PCB solution perfusion continued for an additional 20 min. Normal Krebs-Ringer was then perfused for an additional 40 min and LTP and input–output curves were determined again 60 min or more after tetanic stimulation.

We performed analysis of PCB 153 concentrations by dual capillary column gas chromatography with electron capture detection and sample clean-up on a Florisil column (*22*). Serum PCB levels were measured from dams at the time of weaning and from samples of the Krebs-Ringer made from the generator column for the *in vitro* exposure.

Results

Figure 1 shows averaged raw data traces of the fEPSP before and after tetanic stimulation. The data were recorded from the CA1 region in control slices and slices from animals gestationally and lactationally exposed to PCB 153 at 1.25 mg/kg/day. There was no obvious effect of the PCB exposure on baseline synaptic responses before tetanic stimulation or on the process of posttetanic potentiation (PTP), which is the rapid increase in response amplitude that occurs immediately after tetanic stimulation and results from increased transmitter release due to presynaptic accumulation of calcium. However, the slices from exposed animals show reduced LTP compared to control animals.

Figure 2 shows results from all of the *in vivo* exposure experiments. The bars represent the percent increase above the

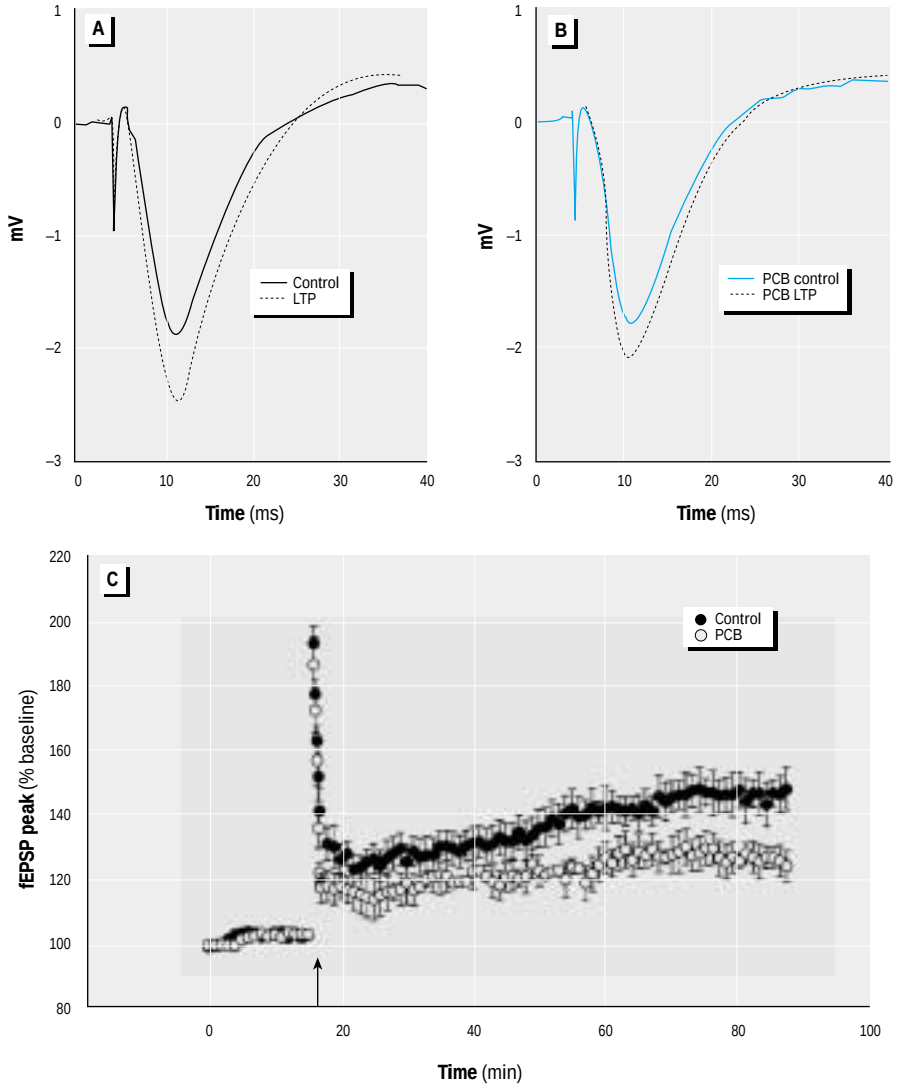

Figure 1. Effects of gestational and lactational exposure to PCB 153 (1.25 mg/kg/day to the dam) on LTP in exposed pups at 30 days of age. (*A*) LTP in control animals. The solid line is the fEPSP before tetanus and the dashed line is the fEPSP to the same intensity stimulation 65 min after a 2-sec tetanic stimulation of the Schaffer collateral pathway. Each trace is the average of the responses elicited over a period of 1 min before and 65 min after the tetanic stimulation. (*B*) is a similar recording from an exposed pup. There is no significant difference in the response before tetanus but there is a reduction in the posttetanic LTP. (*C*) The time course and amplitude of LTP in hippocampal slices obtained from five control and five exposed animals. The error bars show SE for each time point. The arrow indicates the application of tetanic stimulator.

pretetanus baseline response of the response recorded 60 min or more after the tetanic stimulation. Even the lowest dose of PCB 153 resulted in significant reduction in LTP. Although the reduction at 5.0 mg/kg/day did not reach statistical significance because of a large standard error, there was a trend toward a dose-dependent decrease in LTP over these ranges.

Figure 3 shows the effect of *in vitro* application of PCB 153 (indicated by the heavy line in Figure 3C) on fEPSP amplitude, PTP, and LTP. Figure 3A shows an individual fEPSP before and 60 min after induction of LTP from a control slice, whereas Figure 3B is a similar pair of responses from a slice perfused with Krebs-Ringer solution containing PCB. Figure 3C shows pooled data from studies with 11 control and 8 exposed slices prepared from different animals. Perfusion of the PCB-containing solution resulted in a relatively immediate increase (approximately 20%) in the amplitude of the fEPSP, which reversed with washing. This is shown more clearly in Figure 4 in records from one experiment. Although the fEPSP transiently increased somewhat in amplitude, LTP was not maintained in slices perfused with the PCB-containing solution. Figure 5 shows plots of the LTP, expressed as the increase in fEPSP amplitude recorded 60 or more min after tetanic stimulation, obtained from control slices and slices exposed to PCB 153 *in vitro* from 30-day-old animals. Both showed a degree of LTP suppression similar to that observed with the *in vitro* exposures.

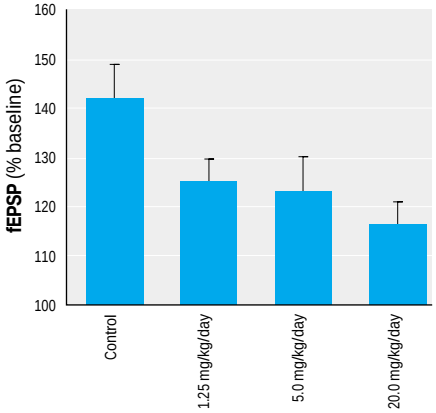

Figure 2. Pooled results of effects of gestational and lactational exposure to PCB 153 at various doses on LTP in the Schaffer Collateral pathway to area CA1. Each bar represents average increase in fEPSP amplitude ± SE recorded for a 1-min period 60 min after tetanic stimulation over that obtained in a 1-min period in the control before tetanization. Results were obtained from five animals. The result from individual animals was determined as the average obtained from multiple hippocampal slices. The values for 1.25 and 20.0 mg/kg/day are significantly different from the control at the level $p < 0.05$.

Figure 6 shows input–output curves for the *in vivo* exposures before and after induction of LTP and demonstrates that PCB 153-exposed animals show a reduced response over the full range of the input–output curve. We did not detect any significant effect on the input–output curve before tetanic stimulation in either the *in vivo* or *in vitro* (not illustrated) exposure.

Serum levels of PCB 153 in dams at the end of exposure were 11 ± 2 ppb in controls; 270 ± 92 ppb in the 1.25-mg/kg/day group; 1,125 ± 490 ppb in the 5-mg/kg/day group; and 2,019 ± 1,911 ppb in the 20-mg/kg/day group. Three determinations of PCB 153 concentration in Krebs-Ringer solution made from distilled water circulated for at least 4 days over the generator column gave concentrations between 0.5 and 1.3 ppb, which is consistent with the conclusion that the concentration would be near the limit of solubility of this congener.

Discussion

These studies add significantly to the accumulating body of evidence that PCB exposure results in decrements in nervous system plasticity without disruption of normal synaptic transmission. These studies also provide a possible experimental basis for the observation that children developmentally exposed to PCBs suffer from reduced IQ.

There is considerable evidence from animal studies that PCB exposure causes altered behavior and reduced learning ability, where exposure can be quantitated, and that human investigations are consistent with the conclusion that PCB exposure early in life causes neurobehavioral decrements (*1–4*). A number of early studies with PCB mixtures demonstrated neurobehavioral effects in rodents (*23–25*). In more recent studies with single congeners, Schantz et al. (*6*) investigated effects of gestational exposure on days 10–66 of rats to PCB 28 (2,4,4´-triCB; 8 or 32 mg/kg/day), 118 (2,3´,4,4´,5-pentaCB; 4 or 16 mg/kg/day), and 153 (16 or 64 mg/kg/day) on adult rat behavior. The authors reported that at higher doses of all three congeners there were delays in acquisition of a working/reference memory task and a T-maze delayed spatial alternation task in females but not males. We used smaller doses of PCB 153 in the present experiments but we used greater exposure time. We studied only males at 30 days of age; Schantz et al. (*6*) studied males and females ≥ 90 days of age. The observations of Schantz et al. (*6*) suggest the possibility that the decrement in LTP might be even greater in females. Alterations of behavior with PCB 153 have also been reported by Holene et al. (*26*). The authors exposed nursing dams to PCB 153 at 5 mg/kg on alternate days between postnatal day 3 and 13 and observed hyperactivity in males.

Several other PCB congeners also reportedly cause changes in learning behavior.

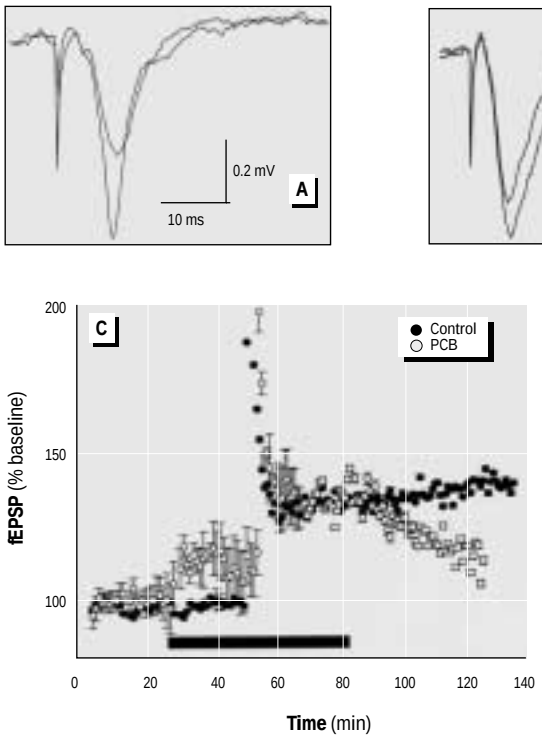

Figure 3. Effects of *in vitro* application of PCB 153 on fEPSP and LTP in CA1. (*A*) fEPSPs before (the smaller trace) and 60 min after (the larger trace) tetanic stimulation from a control slice. (*B*) A similar pair of responses after perfusion of a Krebs-Ringer solution containing PCB 153 beginning 15 min before tetanic stimulation and continuing for 20 min. LTP was therefore measured 40 min after the perfusion was returned to control Krebs-Ringers. (*C*) Pooled results of the effects of *in vitro* application of PCB 153 on fEPSP amplitude. fEPSP amplitude was increased by exposure to PCB 153 even before tetanic stimulation but the increased amplitude was not maintained after washout. Error bars are SEs. The time and duration of PCB perfusion is indicated by the solid line in *C*.

Eriksson and Fredriksson (*7*) reported that neonatal exposure of mice to PCB 52 (2,2´5,5´-tetraCB) affected learning and memory functions in adult animals, although they did not see similar effects of three other congeners [PCBs 28, 118, and 156 (2,3,3´,4,4´,5-hexaCB)] in the same dose range. However, the authors reported changes in spontaneous behavior observed with PCB 28. In a later study the same authors (*27*) demonstrated reduced learning in a swim maze after a single oral dose of PCB 126 (0.46 mg/kg) but no effect of a similar dose of PCB 105 (2,3,3´,4,4´-pentaCB). However, Rice and Hayward (*28*) saw no effect of gestational and lactational exposure of rats to PCB 126 at levels of up to 1 µg/kg/day on multiple fixed interval–fixed ratio and DLR performance. Weinand-Harer et al. (*29*) exposed pregnant rats to 1 mg/kg/day PCB 77 (3,4,3´,4´-tetraCB) or 47 (2,4,2´,4´-tetraCB) for 11 days during gestation; they reported significant differences in the PCB 77-exposed animals from controls in haloperiodol-induced catalepsy and passive avoidance behavior when tested as adults. In monkeys there have not been long-term studies with single congeners, but upon exposure to mixtures several groups demonstrated behavioral effects, including impaired performance on discrimination, delayed spatial alternation, fixed interval, and differential reinforcement of low rate performance (*5*,*30*–*32*). Although the relevance of LTP to some of these behavioral alterations is still unclear and different PCB congeners clearly have different effects, our observations at minimum provide a possible cellular substrate for some of these alterations.

PCBs cause several neurotoxic effects. Shain et al. (*33*) showed that some *ortho*-substituted congeners inhibit tyrosine hydroxylase, the rate-limiting enzyme in synthesis of the important neurotransmitter dopamine. Seegal et al. (*34*) demonstrated reductions in dopamine concentration in monkeys exposed to Aroclor mixtures. A number of *ortho*-substituted congeners cause acute neuronal cell death in cerebellar granule cells (*35*,*36*), perhaps via interference with calcium homeostasis (*37*). Pessah and colleagues [summarized in Fischer et al. (*38*)] showed that several *ortho*-substituted congeners alter calcium transport across microsomal membranes by a ryanodine receptor-mediated pathway, and suggested that this is a common mechanism of *ortho*-substituted PCB toxic actions. Wong et al. (*39*) also explored effects of the tri-*ortho*-substituted PCB 95 (2,2´,3,5´,6-pentaCB) on fEPSPs from hippocampal CA1 slices, and reported that PCB 95 but not PCB 66 (2,3´,4,4´-tetraCB) reduced fEPSP amplitude. They attributed this action to effects of ryanodine receptors. Although there has not been much study of PCBs and LTP, Altmann et al. (*40*) reported that developmental exposure to PCB 77 blocked LTP in visual cortex but not hippocampus. However, PCB 77 should not act at ryanodine receptors. The results of Altmann et al. (*40*) are also inconsistent with our previous observation that PCB 77 blocks LTP in CA1, although our studies were with acute exposure (*16*). We found that all of the major Aroclor mixtures blocked LTP, as did PCB 28 and 77. Further studies are necessary, although it seems unlikely that the effects of PCBs causing neuronal cell death and alterations of dopamine concentrations are due to the same mechanisms that alter LTP. The concentrations of PCBs required for these actions are generally reported to be somewhat greater than those causing a reduction of LTP, and dopamine is not known to have a critical role in LTP in CA1. Gilbert and Crofton (*41*) recently reported that *in vivo* exposure to Aroclor 1254 results in decrements of LTP in the dentate gyrus, which is consistent with our observations in a different hippocampal area.

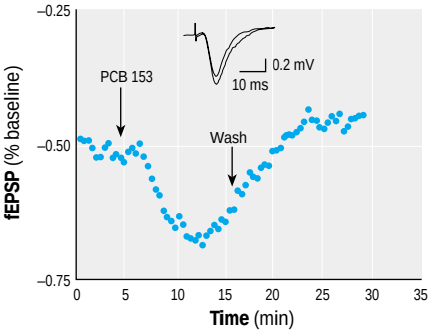

Figure 4. Effects of *in vitro* application of Krebs-Ringer solution containing PCB 153 on fEPSP amplitude from one experiment. The insert shows fEPSPs recorded just before PCB application and just before initiation of wash with normal Krebs-Ringer. No tetanic stimulation was applied during this recording.

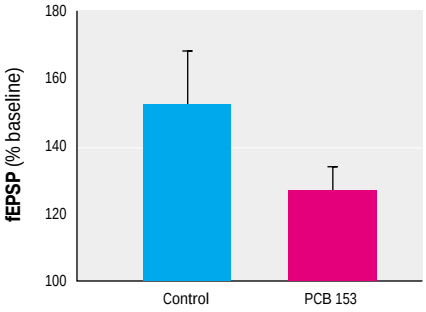

Figure 5. Bar graph plots of LTP amplitude, expressed as percentage increase in fEPSP amplitude over that before tetanic stimulation, recorded in control slices (n = 13) and slices perfused with Krebs-Ringer solution containing PCB 153 (n = 8). The reduction in LTP after *in vitro* exposure to PCB 153 is significant at the $p < 0.05$ level.

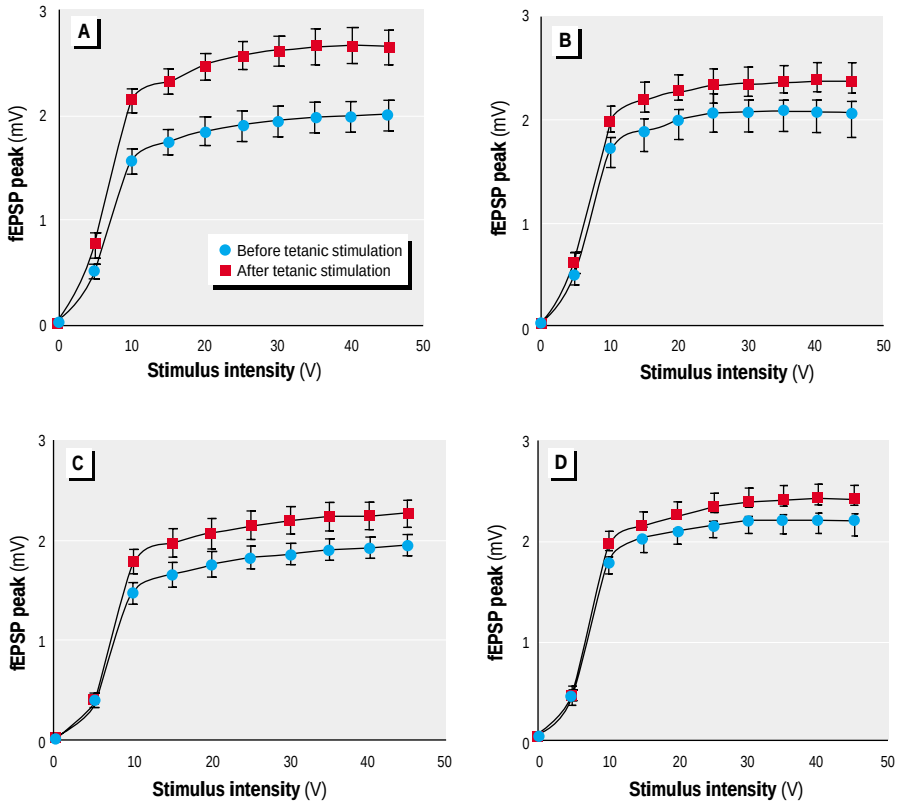

Figure 6. Input–output curves from animals with *in vivo* exposure to PCB 153 before and 60+ min after induction of LTP. (*A*) Control. (*B*) 1.25 mg/kg/day PCB. (*C*) 5.0 mg/kg/day PCB. (*D*) 20.0 mg/kg/day PCB.

The mechanism(s) whereby PCBs block LTP are presently unknown. Whereas the demonstration that both PCB 153 and the mixtures and single congeners previously studied by Niemi et al. (*16*) are effective on acute *in vitro* exposure is consistent with a direct action of PCBs, it is also possible that with *in vivo* exposure they might act indirectly through disruption of thyroid function. Ness et al. (*42*) showed that different congeners have different potencies in reducing total thyroxine levels in rats, with PCB 153 of intermediate potency. However, Desaulniers et al. (*43*), and others reported that PCB 153 exposure results in an increase, not a decrease, in serum thyroid hormone levels. Niemi et al. (*44*) previously showed that hypothyroid animals show reduced LTP.

The rapid and reversible increase in fEPSP amplitude on acute perfusion of PCB 153 was unexpected. It is noteworthy that this effect was transient and was reduced with time even in the continued presence of PCB 153. Somewhat similar effects on hippocampal population responses have been reported by Hong et al. (*45*) and Gilbert and Liang (*46*). It is possible that this action reflects a PCB-induced increase in intracellular calcium concentration in the presynaptic terminal, similar to that which can be induced in isolated cells (*35*,*36*) and would increase transmitter release. The mechanisms responsible for this action will require additional study, but the transient increase did not prevent acute application of PCB 153 from causing a reduction in LTP as measured 40 min after washing with control Krebs-Ringers.

PCB 153 is one of the most persistent congeners; it is widely distributed in humans and the environment. Because it is a poor activator of the Ah receptor it has widely been considered lacking in significant toxicity. Our results suggest that this may not be the case, if indeed LTP is a valid indicator of substances that alter learning ability.

References and Notes

1. Chen Y-CJ, Guo Y-L, Hsu C-C, Rogan WJ. Cognitive development of Yu-Cheng (oil disease) children prenatally exposed to heat-degraded PCBs. JAMA 268:3213–3218 (1992).
2. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls *in utero*. N Engl J Med 335:783–789 (1996).
3. Lonky E, Reihman J, Darvill T, Mather Sr J, Daly H. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 22:198–212 (1996).
4. Winneke G, Bucholski A, Heinzow B, Kramer U, Schmidt E, Walkowiak J, Wiener J-A, Steingruber H-J. Developmental neurotoxicity of polychlorinated biphenyls (PCBs): cognitive and psychomotor functions in 7-month-old children. Toxicol Lett 102–103:423–428 (1998).
5. Rice DC. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. Environ Res 80:S113–S121 (1999).
6. Schantz SL, Moshtaghian J, Ness DK. Spatial learning deficits in adult rats exposed to *ortho*-substituted PCB congeners during gestation and lactation. Fundam Appl Toxicol 26:117–126 (1995).
7. Eriksson P, Fredriksson A. Developmental neurotoxicity of four *ortho*-substituted polychlorinated biphenyls in the neonatal mouse. Environ Toxicol Pharmacol 1:155–165 (1996).
8. Bliss TVP, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol (Lond) 232:332–356 (1973).
9. Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39 (1993).
10. Hori N, Hirotsu I, Davis PJ, Carpenter DO. Long-term potentiation is lost in aged rats but preserved by calorie restriction. Neuroreport 3:1085–1088 (1992).
11. Grant SGN, O'Dell TJ, Karl KA, Stein PL, Soriano P, Kandel ER. Impaired long-term potentiation, spatial learning, and hippocampal development in *fyn* mutant mice. Science 258:1903–1910 (1992).
12. Sakimura K, Kutsuwada T, Ito I, Manabe T, Takayama C, Kushiya E, Yagi T, Aizawa S, Inoue Y, Sugiyama H, et al. Reduced hippocampal LTP and spatial learning in mice lacking NMDA receptor 1 subunit. Nature 373:151–155 (1995).
13. Moser EI, Krobert KA, Moser M-B, Morris RGM. Impaired spatial learning after saturation of long-term potentiation. Science 281:2038–2042 (1998).
14. Altmann L, Weinsberg F, Sveinsson K, Lilienthal H, Wiegand H, Winneke G. Impairment of long-term potentiation and learning following chronic lead exposure. Toxicol Lett 66:105–112 (1993).
15. Hori N, Busselberg D, Matthews MR, Parsons PJ, Carpenter DO. Lead blocks LTP by an action not at NMDA receptors. Exp Neurol 119:192–197 (1993).
16. Niemi WD, Audi J, Bush B, Carpenter DO. PCBs reduce long-term potentiation in the CA1 region of rat hippocampus. Exp Neurol 151:26–34 (1998).
17. Duarte-Davidson R, Wilson SC, Jones KC. PCBs and other organochlorines in human tissue samples from the Welsh population. I: Adipose. Environ Pollut 84:69–77 (1994).
18. Kostyniak PJ, Stinson C, Greizerstein HB, Vena J, Buck G, Mendola P. Relation of Lake Ontario fish consumption, lifetime lactation, and parity to breast milk polychlorobiphenyl and pesticide concentrations. Environ Res 80:S166–S174 (1999).
19. Kafafi SA, Afeefy HY, Ali A, Said HK, Kafafi AG. Binding of polychlorinated biphenyls to the aryl hydrocarbon receptor. Environ Health Perspect 101:422–428 (1993).
20. Sokol RC, Bush B, Wood LW, Jahan-Parwar B. Production of aqueous PCB solutions for environmental toxicology. Chemosphere 24:483–495 (1992).
21. ATSDR. Toxicological Profile for Polychlorinated Biphenyls. Atlanta, GA:Agency for Toxic Substances and Disease Registry, 1997.
22. DeCaprio AP, Tarbell AM, Bott A, Wagemaker DL, Williams RL, O'Hehir CM. Routine analysis of 101 polychlorinated biphenyl congeners in human serum by parallel dual-column gas chromatography with electron capture detection. J Anal Toxicol (in press).
23. Tilson HA, Davis GJ, McLachlan JA, Lucier GW. The effects of polychlorinated biphenyls given prenatally on the neurobehavioral development of mice. Environ Res 18:466–474 (1979).
24. Overmann SR, Kostas J, Wilson LR, Shain W, Bush B. Neurobehavioral and somatic effects of perinatal PCB exposure in rats. Environ Res 44:56–70 (1987).
25. Daly HB, Hertzler DR, Sargent DM. Ingestion of environmentally contaminated Lake Ontario salmon by laboratory rats increases avoidance of unpredictable aversive nonreward and mild electric shock. Behav Neurosci 103:1356–1365 (1989).
26. Holene E, Nafstad I, Utne Skaare J, Sagvolden T. Behavioural hyperactivity in rats following postnatal exposure to sub-toxic doses of polychlorinated biphenyl congeners 153 and 126. Behav Brain Res 94:213–224 (1998).
27. Eriksson P, Fredriksson A. Neurotoxic effects in adult mice neonatally exposed to 3,3´4,4´5-pentachlorobiphenyl or 2,3,3´4,4´-pentachlorobiphenyl: changes in brain nicotinic receptors and behaviour. Environ Toxicol Pharmacol 5:17–27 (1998).
28. Rice DC, Hayward S. Lack of effect of 3,3´4,4´,5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on multiple fixed interval-fixed ratio and DRL performance in rats. Neurotoxicol Teratol 20:645–650 (1998).
29. Weinand-Harer A, Lilienthal H, Bucholski K-A, Winneke G. Behavioral effects of maternal exposure to an orthochlorinated or a coplanar PCB congener in rats. Environ Toxicol Pharmacol 3:97–103 (1997).
30. Levin ED, Schantz SL, Bowman RE. Delayed spatial alteration deficits resulting from perinatal PCB exposure in monkeys. Arch Toxicol 62:267–273 (1988).
31. Schantz SL, Levin ED, Bowman RE, Heironimus MP, Laughlin NK. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. Neurotoxicol Teratol 11:243–250 (1989).
32. Rice DC, Hayward S. Effects of postnatal exposure to a PCB mixture in monkeys on nonspatial discrimination reversal and delayed alternation performance. Neurotoxicology 18:479–494 (1997).
33. Shain W, Bush B, Seegal R. Neurotoxicity of polychlorinated biphenyls: structure-activity relationship of individual congeners. Toxicol Appl Pharmacol 111:33–42 (1991).
34. Seegal RF, Bush B, Brosch KO. Comparison of effects of Aroclors 1016 and 1260 on non-human primate catecholamine function. Toxicology 66:145–163 (1991).
35. Kodavanti PRS, Tilson HA. Structure-activity relationships of potentially neurotoxic PCB congeners in the rat. Neurotoxicology 18:425–442 (1997).
36. Carpenter DO, Stoner CRT, Lawrence DA. Flow cytometric measurements of neuronal death triggered by PCBs. Neurotoxicology 18:507–514 (1997).
37. Kodavanti PRS, Ward TR, McKinney JD, Tilson HA. Inhibition of microsomal and mitochondrial Ca^{2+}-sequestration in rat cerebellum by polychlorinated biphenyl mixtures and congeners: structure-activity relationships. Arch Toxicol 70:150–157 (1996).
38. Fischer LJ, Seegal RF, Ganey PE, Pessah IN, Kodavanti PRS. Symposium overview: toxicity of non-coplanar PCBs. Toxicol Sci 41:49–61 (1998).
39. Wong PW, Joy RM, Albertson TE, Schantz SL, Pessah IN. *ortho*-Substituted 2,2´,3,5´6-pentachlorobiphenyl (PCB 95) alters rat hippocampal ryanodine receptors and neuroplasticity *in vitro*: evidence for altered hippocampal function. Neurotoxicology 18:443–456 (1997).
40. Altmann L, Weinand-Haerer A, Lilienthal H, Wiegand H. Maternal exposure to polychlorinated biphenyls inhibits long-term potentiation in the visual cortex of adult rats. Neurosci Lett 202:53–56 (1995).
41. Gilbert ME, Crofton KM. Developmental exposure to a commercial PCB mixture (Aroclor 1254) produces a persistent impairment in long-term potentiation in the rat dentate gyrus *in vivo*. Brain Res 850:87–95 (1999).
42. Ness DK, Schantz SL, Moshtaghian M, Hansen LG. Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat. Toxicol Lett 68:311–323 (1993).
43. Desaulniers D, Leingartner K, Wade M, Fintelman E, Yagminas A, Foster WG. Effects of acute exposure to PCBs 126 and 153 on anterior pituitary and thyroid hormones and FSH isoforms in adult Sprague Dawley male rats. Toxicol Sci 47:158–169 (1999).
44. Niemi WD, Slivinski K, Audi J, Rej R, Carpenter DO. Propylthiouracil treatment reduces long-term potentiation in area CA1 of neonatal rat hippocampus. Neurosci Lett 210:127–129 (1996).
45. Hong SJ, Grover CA, Safe SH, Tiffany-Castiglioni E, Frye GD. Halogenated aromatic hydrocarbons suppress CA1 field excitatory postsynaptic potentials in rat hippocampal slices. Toxicol Appl Pharmacol 148:7–13 (1998).
46. Gilbert ME, Liang D. Alterations in synaptic transmission and plasticity in hippocampus by a complex PCB mixture, Aroclor 1254. Neurotoxicol Teratol 20:383–389 (1998).